General

Guideline Title

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 1. 70 p. (Technology appraisal guidance; no. 383).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 47 p. (Technology appraisal guidance; no. 143).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (NSAIDs). Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their National Health Service (NHS) clinician consider it appropriate to stop.

Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- A reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- A reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more

Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response.

When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Ankylosing spondylitis
- Non-radiographic axial spondyloarthritis

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis

Target Population

Adult patients with either severe active ankylosing spondylitis or severe non-radiographic axial spondyloarthritis whose disease has responded

inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (NSAIDs)

Interventions and Practices Considered

1. Tumour necrosis alpha (TNF)-alpha inhibitors
    - Adalimumab
    - Certolizumab pegol
    - Etanercept
    - Golimumab
    - Infliximab
2. Assessment of treatment response using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score or visual analogue scale (VAS) pain score

Major Outcomes Considered

- Clinical effectiveness
    - Multiple domain response criteria: (e.g., Assessment of Ankylosing Spondylitis [ASAS] 20, ASAS 40, ASAS 5/6 and ASAS partial remission)
    - Disease activity (e.g., Bath Ankylosing Spondylitis Disease Activity Index [BASDAI])
    - Functional capacity (e.g., Bath Ankylosing Spondylitis Functional Index [BASFI])
    - Disease progression (e.g., modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS])
    - Pain (e.g., visual analogue scale [VAS] scores)
    - Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis)
    - Symptoms of extra-articular manifestations (including anterior uveitis, inflammatory bowel disease and psoriasis)
    - Health-related quality of life (e.g., EuroQol 5 dimensional [EQ-5D])
    - Rates of treatment discontinuation and withdrawal
    - Adverse events
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Assessment Report for this technology appraisal was prepared by the Centre for Reviews and Dissemination/Centre for Health Economics (CRD/CHE) Technology Assessment Group, University of York (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Inclusion Criteria

Two reviewers independently screened all titles and abstracts. Full manuscripts of any titles/abstracts that were relevant were obtained where possible and the relevance of each study assessed by two reviewers according to the criteria below. Any discrepancies were resolved by consensus and, when necessary, a third reviewer was consulted. Studies available only as abstracts were included.

Study Design

For the review of clinical efficacy randomised controlled trials (RCTs) were eligible, including any open-label extensions of RCTs. Adverse events

data were sought from existing reviews and other appropriately large studies. For studies of natural history, long-term effectiveness, adherence, and sequential use, published analyses based on large and long-term data sets (including studies of registry data) were eligible.

Interventions

Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or any of their biosimilars were eligible.

Comparators

Relevant comparators were conventional management strategies (either with or without placebo) and also the different tumour necrosis factor (TNF)-alpha inhibitors listed above (i.e., head-to-head trials).

Participants

Studies of adults with either severe active ankylosing spondylitis or severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation (such as elevated C-reactive protein levels or a positive magnetic resonance imaging [MRI] scan) were eligible. Patients with predominantly peripheral spondyloarthritis were excluded. Data relating to serious adverse effects associated with anti-TNF agents used in other indications were also considered.

Outcomes

Studies reporting the following outcomes were eligible:

- Multiple domain response criteria: (e.g., Assessment of Ankylosing Spondylitis [ASAS] 20, ASAS 40, ASAS 5/6 and ASAS partial remission)
- Disease activity (e.g., Bath Ankylosing Spondylitis Disease Activity Index [BASDAI])
- Functional capacity (e.g., Bath Ankylosing Spondylitis Functional Index [BASFI])
- Disease progression (e.g., modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS])
- Pain (e.g., visual analogue scale [VAS] scores)
- Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis)
- Symptoms of extra-articular manifestations (including anterior uveitis, inflammatory bowel disease and psoriasis)
- Health-related quality of life (e.g., EuroQol 5 dimensional [EQ-5D])
- Rates of treatment discontinuation and withdrawal
- Adverse events

For adverse events the evaluation specifically focussed on known possible adverse events of anti-TNFs, such as reactivation of latent tuberculosis, malignancies, non-melanoma skin cancer, severe infections, congestive heart failure, and injection site reactions. Withdrawals due to adverse events, and events categorised as serious adverse events were also evaluated.

Searches

The following databases were searched for relevant clinical and cost-effectiveness research:

- MEDLINE
- EMBASE
- CINAHL Plus
- Science Citation Index
- ClinicalTrials.gov
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- International Prospective Register of Systematic Reviews (PROSPERO)
- Health Technology Assessment database
- Conference Proceedings Citation Index - Science
- National Guideline Clearinghouse (NGC)
- National Health Service (NHS) Evidence
- NHS Clinical Knowledge Summaries
- NHS Economic Evaluation Database (EED)

The terms for search strategies were identified through discussion within the research team, by scanning the background literature and browsing the MEDLINE Medical Subject Headings (MeSH). No date or language limits were applied. As several databases were searched, some degree of duplication resulted. To manage this issue, the titles and abstracts of bibliographic records were imported into Endnote bibliographic management software to remove duplicate records. The full search strategies used in each database are listed in Appendix 1 of the Assessment Report.

Assessment of Cost-effectiveness

Systematic Review of Existing Cost-effectiveness Evidence

Methods

An initial systematic search was undertaken in the NHS EED using a combination of technology names and disease terms. Further searches were undertaken in MEDLINE and EMBASE for modelling and utility studies using disease terms only (as known references were not identified from the initial search in NHS EED). Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included in the review of existing economic literature. No language and date limits were initially applied, although eligibility of studies was subsequently restricted to those reporting results which were specific to the UK. Full details of the search strategies used are reported in Appendix 1 of the Assessment Report.

In addition, as part of the current multiple technology assessment (MTA) process, each manufacturer submitted *de-novo* evidence on the cost-effectiveness of the anti-TNFs in line with their respective indications for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis. These submissions are reviewed and the findings compared with those found in the review of previously published studies.

Results of Review of Existing Cost-effectiveness Evidence

The combined searches retrieved 210 citations. A total of six UK studies reporting on the cost-effectiveness of anti-TNFs for the treatment of ankylosing spondylitis were identified. No previously published studies were identified for patients with non-radiographic axial spondyloarthritis.

Number of Source Documents

Clinical Effectiveness

- Seventeen randomised controlled trials (RCTs) with open-label extension studies (71 further open-label study references) were included.
- Additional 7 RCTs without open-label extension studies were also included.

Refer to Figure 1 in the Assessment Report (see the "Availability of Companion Documents" field) for a flowchart showing the number of studies identified and included.

Cost-effectiveness

- A total of 5 existing studies met the inclusion criteria.
- Four manufacturers' submissions were included.
- An independent Assessment Group's model was also included.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Assessment Report for this technology appraisal was prepared by the Centre for Reviews and Dissemination/Centre for Health Economics (CRD/CHE) Technology Assessment Group, University of York (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Data Extraction

Data relating to study design, outcome results and quality were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, and when necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study. Data were also extracted from the manufacturer submissions when they were not available from other sources. Clinicaltrials.gov records and relevant U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) reports were also used to extract any missing data. Where data could only be estimated from graphs, the estimates used in the previous assessment report were used when available. In light of the multi-domain outcomes which incorporated pain scores (the Assessment of Ankylosing Spondylitis [ASAS] and Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] outcomes), it was decided that pain scores on their own would not be extracted.

Critical Appraisal

The quality of randomised controlled trials (RCTs) was assessed using the Cochrane risk of bias tool, with additional assessments made for baseline imbalance of important prognostic indicators. The relevant prognostic and treatment response indicators were identified from both published research and clinical advice. The risk of bias assessments were performed by one reviewer, and independently checked by a second. Disagreements were resolved through consensus, and when necessary, a third reviewer was consulted. Open-label extension studies were evaluated based on the imputation methods and patient withdrawal criteria used.

Methods of Data Synthesis

Results of the data extraction in terms of study characteristics and quality assessment are presented in tables in the Assessment Report and summarised narratively. Results of open-label studies, drug survival and switching studies, and natural history studies were also summarised narratively. Since several of the RCTs were placebo-controlled up to 24 weeks, only time points beyond 24 weeks were evaluated in the open-label studies. Adverse event data from the RCTs were pooled when enough data was identified, otherwise the adverse event data and the other studies relating specifically to adverse events were summarised narratively.

Clinical effectiveness data were synthesised using Bayesian meta-analysis methods. The main analysis was of outcomes reported from 10 to 16 weeks. A sensitivity analysis was done of outcomes reported from 24 to 30 weeks.

Refer to Section 4 of the Assessment Report for additional information about the clinical effectiveness analysis.

Assessment of Cost-effectiveness

Assessment of Published Cost-effectiveness Studies

Section 5.1 of the Assessment Report provides an overview of existing cost-effectiveness evidence and an assessment of the relevance of the data from the perspective of the UK National Health Service (NHS). The differences in the approaches and assumptions used across the studies are examined in order to explain any discrepancies in the findings and to identify key areas of remaining uncertainty. The findings from the review provide the basis for the development of a new decision-analytic model reported in Section 7 of the Assessment Report, 'Assessment of cost-effectiveness: York Economic Assessment'.

Summary of Manufacturers' de-novo Submissions

Overview of Adalimumab Model

The economic model presented by the manufacturer of adalimumab compared the cost-effectiveness of adalimumab vs. conventional therapy and other licensed anti-tumour necrosis factors (TNFs) for non-radiographic axial spondyloarthritis and ankylosing spondylitis. Separate state-transition

models were developed for the two indications separately based on the ASAS guidelines for the use of anti-TNFs. All patients were assumed to take conventional therapy/background therapy (e.g., non-steroidal anti-inflammatory drugs [NSAIDs]) during the modelled horizon and also receive one of the licensed anti-TNFs or placebo (conventional therapy only). Specifically, patients were assumed to stay on therapy as long as they had an adequate therapeutic response (i.e., ASAS 40 for non-radiographic axial spondyloarthritis and ASAS 20 for ankylosing spondylitis) and patients were assumed to discontinue therapy when insufficient response occurred. Discontinuations due to adverse events (AEs) or reasons other than therapeutic failures were also included. The model consists of a short-term component (first 12 weeks) and a longer term component to estimate lifetime costs-effectiveness (40 years). In common with previously published models, the model was based on the estimation of BASDAI and BASFI scores over time.

Overview of Certolizumab Model

The economic model presented by the manufacturer of certolizumab compared the cost-effectiveness of certolizumab vs. conventional therapy and other licensed anti-TNFs for non-radiographic axial spondyloarthritis and ankylosing spondylitis. Separate Markov cohort models were developed for the two indications separately based on the subpopulations of the RAPID-axSpA trial. Separate analyses were argued to be necessary given that the comparators differed for each subpopulation. Analyses performed for the ankylosing spondylitis subpopulation consisted of all patients with ankylosing spondylitis from the RAPID-axSpA study, including those who were anti-TNF therapy-experienced or naïve. The non-radiographic axial spondyloarthritis subpopulation consisted of anti-TNF therapy-naïve patients only, as there were no anti-TNF therapy-experienced patients in this subpopulation.

The model consists of a short-term component and a longer term component to estimate lifetime costs-effectiveness. The duration of the short-term component varied between the models used for the ankylosing spondylitis and the non-radiographic axial spondyloarthritis subpopulations based on the response endpoint assumed. Response was assessed at 24 weeks in the ankylosing spondylitis subpopulation which was argued by the manufacturer to be in accordance with clinical practice as indicated by key British opinion leaders. For the non-radiographic axial spondyloarthritis subpopulation, response assessment was assumed at 12 weeks since comparator data were only available at that time point.

Overview of Etanercept Model

The economic model submitted by the manufacturer of etanercept compared the cost-effectiveness of etanercept vs. conventional therapy and other licensed anti-TNFs for ankylosing spondylitis, non-radiographic axial spondyloarthritis, and a combined population (axSpA). The results for the combined population are not summarised in the review but are reported separately in the manufacturer submission. The model is based on a lifetime time-horizon and costs and benefits are discounted at an annual rate of 3.5%. The reference year for costs was reported to be 2014.

The model was based on a patient-level simulation model based on a discrete event simulation (DES). The analysis was conducted from a NHS/Personal Social Services (PSS) perspective. Data to populate the model were derived from key clinical trials for etanercept and results of a clinical systematic review, mixed treatment comparison (MTC) and in a separate analysis presented for the non-radiographic axial spondyloarthritis population, a match adjusted indirect comparison (MAIC). The model structure was reported to be developed in accordance with current OMERACT (Outcome Measures in Rheumatology) guidance and was constructed around BASDAI and BASFI in line with other published studies.

Overview of Golimumab and Infliximab Model

The economic models submitted by the manufacturer of golimumab and infliximab compared the cost-effectiveness of golimumab and infliximab vs. conventional therapy and other licensed anti-TNFs for ankylosing spondylitis. Although the manufacturer made separate submissions for golimumab and infliximab, the model structures and data sources used to inform the economic models are identical across the submissions. Hence, the review focuses on the specific submission for golimumab but also considers key data sources and assumptions specific to infliximab. The model base-case is based on a lifetime time-horizon (approximately 60 years) and costs and benefits are discounted at an annual rate of 3.5%. A NHS and PSS perspective is used for costs. The reference year for costs was reported to be 2012/13.

The manufacturer's cost-effectiveness model was based on a short-term decision tree (based on an assessment of BASDAI 50 response at 12 weeks in the base-case) and a longer term Markov model.

The proportion of patients achieving BASDAI 50 at week 12 (+/-2 weeks) for each TNF-alpha inhibitor was obtained from a systematic review and MTC undertaken by the manufacturer.

Refer to Sections 5, 6, and 7 of the Assessment Report for additional information about the manufacturers' models and the independent Assessment Group's model.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an Assessment Report. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the Appraisal Consultation Document (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the Final Appraisal Determination (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

Although the models from the companies and the Assessment Group all used changes in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores to model costs and utilities, the underlying assumptions in each model were very different. The Assessment Group divided the models into 3 key stages: the probability of initial response, the size of initial response for 'responders' and 'non-responders', and the long-term trajectory of BASDAI and BASFI scores (conditional on response status). The Committee noted the Assessment Group's criticism that some of the company models combined the latter 2 stages. The Committee decided to use

the Assessment Group's model for its decision-making.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

In the Assessment Group's model, 'responders' had lower baseline BASDAI and BASFI scores compared with 'non-responders' (a difference that was reduced in scenario 2), implying that people with more severe disease did not benefit as much from tumour necrosis factor (TNF)-alpha inhibitors as people with less severe disease. The Committee concluded that there was no evidence to suggest that people with severe disease were less likely to have a clinically meaningful benefit than those with less severe disease.

The Committee agreed with the Assessment Group's assumption that physical function (measured by BASFI) continues deteriorating during TNF-alpha inhibitor treatment, but at a slower rate compared with the natural history of the disease. However, it disagreed with the Assessment Group's assumption that a TNF-alpha inhibitor's effect on progression is delayed until year 4.

The Assessment Group presented 2 alternative base-case cost-effectiveness analyses to reflect their uncertainty about what happens when a patient stops TNF-alpha inhibitor treatment (the 'rebound' assumption). The Committee concluded that rebound to baseline was the most plausible assumption and considered the incremental cost-effectiveness ratios (ICERs) from this analysis.

Sequential use of TNF-alpha inhibitors was not modelled. The Committee noted that some patients would remain on a sub-optimal treatment if they were unable to switch, at a comparable cost but with decreased quality-adjusted life years (QALYs).

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee was aware that potential differences between the TNF-alpha inhibitors in their effects on extra-articular manifestations may have cost implications, but noted that there was insufficient evidence to incorporate extra-articular manifestations into the cost-effectiveness analysis. However, the Committee concluded that because the TNF-alpha inhibitors had been considered as a class, the choice of treatment for both conditions should be based on clinical appropriateness, which may include consideration of associated conditions.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

There are no specific groups of people for whom the technology is particularly cost effective.

What Are the Key Drivers of Cost-effectiveness?

The difference in the ICERs between the individual TNF-alpha inhibitors was driven entirely by different acquisition and administration costs.

ICERs were sensitive to assumptions about the magnitude of the difference in baseline BASDAI/BASFI scores between 'responders' and 'non-responders'.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

For ankylosing spondylitis the ICERs for adalimumab, certolizumab pegol, etanercept and golimumab compared with conventional care ranged from about £19,200 per QALY gained for certolizumab pegol (with the patient access scheme) to £21,600 per QALY gained for etanercept in the Assessment Group's base case (assuming rebound to baseline). The Committee concluded that these ICERs were all within the range considered to be a cost-effective use of National Health Service (NHS) resources.

The ICERs for infliximab for ankylosing spondylitis were about £40,600 and £36,800 per QALY gained compared with conventional care, using the original and biosimilar prices respectively, in the Assessment Group's base case. However, the Committee noted comments received in response to the appraisal consultation document about the infusion cost of infliximab and the lower prices of the biosimilar versions of infliximab as a result of the tendering process. The Committee also discussed the new ICERs, presented by the companies marketing biosimilar versions of infliximab in response to the appraisal consultation document, that used lower prices to reflect the tendering process that was taking place during the consultation period. The Committee therefore concluded that infliximab could be recommended as an option for treating adults with ankylosing spondylitis.

For non-radiographic axial spondyloarthritis the ICERs for adalimumab, certolizumab pegol and etanercept compared with conventional care ranged from about £28,200 for certolizumab pegol (including the patient access scheme) to £29,800 for etanercept per QALY gained, compared with conventional care. The Committee referred to the conclusion that the benefit of TNF-alpha inhibitors was potentially underestimated in the clinical trials. It also noted that the Assessment Group's assumption of a slower disease progression rate in non-radiographic axial spondyloarthritis compared with ankylosing spondylitis was not confirmed by the clinical experts, and that this would in part have driven the increase in ICERs compared with ankylosing spondylitis. Considering both of these issues, the Committee considered that the most plausible ICERs were likely to be

below those presented by the Assessment Group and the Committee concluded that adalimumab, certolizumab pegol and etanercept were within the range that would be considered a cost-effective use of NHS resources.

The Committee noted the limited clinical-effectiveness data available for sequential TNF-alpha inhibitor use and concluded that it had insufficient cost-effectiveness evidence to allow it to recommend sequential use of TNF-alpha inhibitors as a cost-effective use of NHS resources.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination (FAD).

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturers of tumour necrosis factor (TNF)-alpha inhibitors and a review of these submissions by the Assessment Group. The main clinical effectiveness evidence came from randomised controlled trials (RCTs). For cost-effectiveness, the Appraisal Committee considered economic models submitted by the manufacturers and the Assessment Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Ankylosing spondylitis and non-radiographic axial spondyloarthritis result in the same level of pain, reduced function and poor quality of life. Early treatment is important in order to prevent or delay progressive and irreversible damage, which could ultimately cause someone to need a wheelchair or be unable to get out of bed.
- Patient experts reported that use of tumour necrosis factor (TNF)-alpha inhibitors to treat both ankylosing spondylitis and non-radiographic axial spondyloarthritis had completely changed some people's lives by restoring mobility and reducing pain, and could allow people to continue working and fulfil parental and carer duties.

Potential Harms

The summary of product characteristics lists the following adverse reactions:

- *Adalimumab*: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache, musculoskeletal pain, hepatitis B reactivation, various malignancies and serious haematological, neurological and autoimmune reactions

- *Certolizumab pegol*: infections (including sepsis, pneumonia, tuberculosis, invasive fungal and opportunistic infections), blood and lymphatic system malignancies (including lymphoma and leukaemia), lupus-like syndrome, injection site reactions (erythema, itching, haematoma, pain or swelling), and hepatitis B reactivation
- *Etanercept*: infections (including upper respiratory infections, bronchitis, bladder infections and skin infections, as well as serious infections such as sepsis), injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), allergic reactions, development of auto-antibodies, itching, fever, various malignancies and serious haematological, neurological and autoimmune reactions
- *Golimumab*: infections (including sepsis, pneumonia, tuberculosis, and invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematological reactions
- *Infliximab*: infections (including upper respiratory tract infections, sepsis, opportunistic infections and tuberculosis), hepatitis B reactivation, congestive heart failure, serum sickness (delayed hypersensitivity reactions), haematological reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, hepatosplenic T-cell lymphoma, and serious infusion reactions. Adverse reactions for biosimilar versions of infliximab (Inflectra, Remsima) are the same as for infliximab.
- The Committee heard from clinical experts that tumour necrosis factor (TNF)-alpha inhibitors are well tolerated in both conditions, and that people rarely stop treatment because of adverse events. It concluded that the clinical characteristics of the patient would need to be considered when choosing a TNF-alpha inhibitor.

For full details of side effects and contraindications, see the summaries of product characteristics.

Contraindications

Contraindications

For full details of side effects and contraindications, see the summaries of product characteristics.

Qualifying Statements

Qualifying Statements

- The recommendations in this guidance represent the view of the National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.
- Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the National Health Service (NHS) Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales

must usually provide funding and resources for it within 3 months of the guidance being published.

- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has ankylosing spondylitis and the doctor responsible for their care thinks that adalimumab, certolizumab pegol, etanercept, golimumab or infliximab is the right treatment (or a patient has non-radiographic axial spondyloarthritis and the doctor responsible for their care thinks that adalimumab, certolizumab pegol or etanercept is the right treatment), it should be available for use, in line with NICE's recommendations.
- The Department of Health and Merck, Sharp & Dohme have agreed that golimumab will be available to the NHS with a patient access scheme which makes it available with a discount. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. Any enquiries from NHS organisations about the patient access scheme should be directed to christopher.oregan@merck.com. The Department of Health and UCB Pharma have agreed that certolizumab pegol will be available to the NHS with a patient access scheme. UCB Pharma will provide the first 12 weeks of certolizumab pegol free of charge, which is equivalent to 10 vials. Any enquiries from NHS organisations about the patient access scheme should be directed to oana.purcaru@ucb.com.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 1. 70 p. (Technology appraisal guidance; no. 383).

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

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Guideline Committee

Appraisal Committee

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 47 p. (Technology appraisal guidance; no. 143).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Resource impact report. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb. 11 p. (Technology appraisal guidance; no. 383). Available from the NICE Web site .
- TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Resource impact template. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb. (Technology appraisal guidance; no. 383). Available from the NICE Web site .
- Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E, Moe-Byrne T, Fox D, Marzo-Ortega H, Kay L, Woolacott N, Palmer S. TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233). York (UK): Centre for Reviews and Dissemination/Centre for Health Economics (CRD/CHE) Technology Assessment Group, University of York; 2014. 371 p. Available from the NICE Web site .

Patient Resources

The following is available:

- TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Information for the public. London (UK): National Institute for Health and are Excellence (NICE); 2016 Feb. 3 p. (Technology appraisal guidance; no. 383). Available from the NICE Web site . Also available for download in ePub and eBook formats from the NICE Web site . Also available in Welsh from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on August 7, 2008. This summary was updated by ECRI Institute on August 20, 2009, following the U.S. Food and Drug Administration advisory on Tumor Necrosis Factor (TNF) blockers. This summary was updated by ECRI Institute on October 12, 2011 following the U.S. Food and Drug Administration (FDA) advisory on Tumor Necrosis Factor-alpha (TNFα) Blockers. This summary was updated by ECRI Institute on May 18, 2016.

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